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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/378,577	08/20/1999	WENYUAN SHI	60307-5001	9309

29585 7590 04/25/2005

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/378,577	SHI ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The appeal brief filed on 10-21-2003 is acknowledged. However, based upon the review of the record the finality of the Office action mailed on 7-25-2002 is withdrawn in light of the new claim rejections outlined below.

Claims 1-4, 6-10, 12 and 17 are pending and currently under examination.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim1-4, 6-10, 12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ma et al. (European Journal of Immunology 1944, Vol. 24(1), pages 131-138) iv view of Adair et al. (U.S. Patent 5,877,293) is maintained for reasons of record.

Applicant argues:

1. Ma et al. do not teach or suggest the present invention.

2. Ma et al. teaches away from using the method provided by the instant invention.

3. Ma et al. is directed **primarily** to expressing a murine IgG1 antibody, Guy's 13, in transgenic plants.

4. Guy's 13 prevents the adherence and colonization of *S. mutans in vivo*.

5. Ma et al. disclose that the Fc-mediated functions of the mAB were not essential, as the F(ab')2 portion was as protective as protective as the intact IgG and that while the maintenance of bivalent antigen binding was required for the prevention of colonization of *S. mutans in vivo*, the functional Ig regions that are involved in the complement binding and optimization through cellular interactions are not essential. This illustrates that epitope binding is critical to the protective function of Guy's 13 whereas the Fc-mediated functions are dispensable.

6. The Office states that ma disclosed IgG based antibodies and these IgG based antibodies "by their very nature stimulate a humoral immune response regardless of the motivation behind its application".

7. An obviousness rejection has to rely on what is taught by the art, not what is inherent in the art.

8. Ma et al. do not teach or suggest the use of an antibody that functions through specific binding **and via eliciting a humoral response**.

9. One of skill in the art would not believed that in order to treat or prevent dental caries, he or she should use antibodies that function via specifically binding to a cariogenic organism **and via eliciting a humoral response**.

10. Based on Ma's disclosure one of skill in the art would have used antibodies that have the same epitope specificity as Guy's 13 but would not have realized that using antibodies eliciting a humoral immune response could also provide a protective effect.

11. In order for an IgG antibody to trigger a humoral immune response, it has to be associated with the appropriate (same species) immune system. Hence, the antibodies disclosed by Ma et al. would not have induced a humoral response.

12. The disclosure of Adair et al. does cure the deficiency of Ma et al. since it does not teach or suggest using chimeric antibodies to treat dental caries, especially by eliciting a humoral immune response.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's arguments are predicated that Ma et al. do not specifically disclose the use of chimeric monoclonal that specifically bind a cariogenic organism **and elicit a humoral immune response** to treat or prevent dental caries. As outlined previously, Ma et al. disclose methods for the production of chimeric IgG based (as well as others) monoclonal antibodies against *Staphylococcus mutans* in tobacco plants to use in the treatment of dental caries in humans and other mammals (see page 131, second paragraph). Ma et al. differs from the claimed invention in that both the heavy and light chains of the chimeric monoclonal antibodies are derived from murine antibodies. However, Adair et al. disclose methods for the production of chimeric antibodies where the light chains are derived from murine antibodies and the heavy chains are derived from human antibodies. Consequently, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the methods of Adair et al. to "humanize" the chimeric antibodies disclosed in the methods of Ma et al. in order to take

advantage of the reduced antigenicity and increased therapeutic effectiveness of "humanized" chimeric antibodies. Contrary to Applicant's assertion, one of skill in the art would recognize that the disclosure of Ma et al. teaches methods of using chimeric monoclonal antibodies to treat dental caries and would look to the disclosure of Adair et al. for methods of humanizing said antibodies.

With regard to Applicants assertion that Ma et al. teaches away from the instant invention since they disclose that the Fc-mediated functions of the mAB were not essential, as the F(ab')2 portion was as protective as protective as the intact IgG and that while the maintenance of bivalent antigen binding was required for the prevention of colonization of *S. mutans in vivo*, the functional Ig regions that are involved in the complement binding and optimization through cellular interactions are not essential. This illustrates that epitope binding is critical to the protective function of Guy's 13 whereas the Fc-mediated functions are dispensable: Ma et al. disclose multiple forms of the Guy's 13 antibody including Guy's 13 IgG1 with the original gamma heavy chain (see page 132).

With regard to Applicant's assertion that an obviousness rejection has to rely on what is taught by the art, not what is inherent in the art: Applicant is reminded that the express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). Under the principles of inherency, if a prior art device, in its

normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986). Additionally Applicant is reminded "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best 562* F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

New Claim Rejections

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-10, 12 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to chimeric monoclonal antibodies that specifically bind to a cariogenic organism capable of stimulating a humoral immune response in an animal *to* an

antigen displayed by said cariogenic organism. In other words, the humoral immune response generated is to the cariogenic organism not the chimeric monoclonal antibody.

The claims are drawn to a vast genus of chimeric monoclonal antibodies. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of *chimeric monoclonal antibodies*, Applicant must adequately describe the antigenic determinants (immunoepitopes) that give rise to the production of antibodies that not only bind to a given cariogenic organism but also elicit a humoral immune response directed against an antigen displayed by said cariogenic organism.

However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of *chimeric monoclonal antibodies* to which the claims are drawn, such as a correlation between the structure of the immunoepitope its recited function (to bind to and elicit a humoral immune response directed against a given cariogenic organism, so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of *chimeric monoclonal antibodies*. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential

amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of *chimeric monoclonal antibodies* capable of binding to and eliciting a humoral immune response in a mammal to a given cariogenic organism.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings

or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include

any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of *chimeric monoclonal antibodies* capable of binding to and eliciting a humoral immune response in a mammal to a given cariogenic organism. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer.

Claims 1-4, 6-10, 12 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using chimeric monoclonal antibodies with binding specificity to cariogenic to treat/prevent dental, does not reasonably provide enablement for methods of treating/preventing dental caries utilizing *chimeric monoclonal antibodies* capable of binding to and eliciting a humoral immune response in a mammal to a given cariogenic organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The rejected claims are drawn to methods of using *chimeric monoclonal antibodies* capable of binding to and eliciting a humoral immune response in a mammal to a given cariogenic organism. However, Applicant has failed to demonstrate chimeric monoclonal

antibodies that are capable of eliciting the claimed immune response (a humoral immune response directed against the cariogenic organism itself not the antibody). While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an

epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a specific immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of specific immune responses, the specification, as filed, does not provide enablement for methods of using *chimeric monoclonal antibodies* capable of binding to and eliciting a humoral immune response in a mammal to a given cariogenic organism.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Robert A. Zeman
April 21, 2005